Seizure 25 (2015) 181–183

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Short communication

Role of the gluten-free diet on neurological-EEG findings and sleep disordered breathing in children with celiac disease

P. Parisi [a], N. Pietropaoli [a], A. Ferretti [a], R. Nenna [b], G. Mastrogiorgio [a], M. Del Pozzo [a], L. Principessa [a], M. Bonamico [b], M.P. Villa [a,*]

[a] Pediatric Sleep Disease Centre, Child Neurology, NESMOS Department, School of Medicine and Psychology, Sapienza University of Rome, S. Andrea Hospital, Via di Grottarossa 1035-39, 00189 Rome, Italy
[b] Celiac Disease and Malabsorptive Diseases Unit, Department of Pediatrics, Sapienza University, Viale Regina Margherita 324, 00161 Rome, Italy

ARTICLE INFO

Article history:
Received 10 July 2014
Received in revised form 16 September 2014
Accepted 30 September 2014

Keywords:
Celiac disease
Gluten-free diet
Headache
Electroencephalographic abnormalities
Sleep disordered breathing

ABSTRACT

Purpose: To determine whether celiac children are at risk for EEG-neurological features and sleep disordered breathing (SDB), and whether an appropriate gluten-free diet (GFD) influences these disorders.
Methods: We consecutively enrolled 19 children with a new biopsy-proven celiac disease (CD) diagnosis. At CD diagnosis and after 6 months of GFD, each patient underwent a general and neurological examination, an electroencephalogram, a questionnaire about neurological features, and a validated questionnaire about SDB: OSA (obstructive sleep apnea) scores < 0 predict normality; values > 0 predict OSA.
Results: At CD diagnosis, 37% of patients complained headache that affected daily activities and 32% showed positive OSA score. The EEG examinations revealed abnormal finding in 48% of children. After 6 months of GFD headache disappeared in 72% of children and EEG abnormalities in 78%; all children showed negative OSA score.
Conclusion: According to our preliminary data, in the presence of unexplained EEG abnormalities and/or other neurological disorders/SDB an atypical or silent CD should also be taken into account.

1. Introduction

Celiac disease (CD) is a chronic disorder of the small intestine that occurs in genetically predisposed individuals, with a prevalence of 1.16%.[1]

Although its target organ is the gut, CD is a systemic disorder that involves many other tissues such as nervous system.[2]

Diaconu et al. in 2013 studied the incidence of neurologic manifestations in children with CD showing that one-third of children presented one or more neurologic symptoms as the onset manifestation of CD.[3]

Celiac crisis presenting with status epilepticus and encephalopathy in the absence of profound GI symptom has been recently described.[4]

A meta-analysis of the few evidence-based data available on these disorders in children showed that the relative risk of epilepsy in individuals with CD, and of CD in individuals with epilepsy, compared with the general population, was 2.1 and 1.7, respectively. In the vast majority of these patients, wakefulness EEGs revealed focal abnormalities, mainly localized in one or both occipital regions.[5]

No studies have investigated yet the prevalence of neuronal hyperexcitability and subclinical electroencephalic (EEG) abnormalities in asymptomatic children and adolescents with newly diagnosed CD before the introduction of a gluten-free diet (GFD), and in particular any changes following the introduction of the diet.

On the other hand, studies related to the presence of sleep disordered breathing (SDB) in CD children have not been published yet. SDB is a continuum ranging from primary snoring to obstructive sleep apnea (OSA), which is associated with gas exchange abnormalities and significant sleep fragmentation and affects 1–5.7% of children.[6] SDB is characterized by inflammation, neurological features and autonomic alterations. In our Pediatric Department there is a referral Pediatric Sleep Centre, so we usually investigate SDB by a validated simple questionnaire in different groups of patients, also in children at CD diagnosis.

* Corresponding author. Tel.: +39 0633775358; fax: +39 0633775941.
E-mail address: mariapia.villa@uniroma1.it (M.P. Villa).

http://dx.doi.org/10.1016/j.seizure.2014.09.016
1059-1311/

We aimed to determine whether newly diagnosed celiac children are at risk for EEG-neurological features and SDB, and whether an appropriate GFD influences these disorders.

2. Materials and methods

Nineteen young patients (16 female and 3 male, mean age at diagnosis 9.82 ± 4.09 years, range 3–17 years) with a new biopsy-proven CD diagnosis on a free diet were consecutively included in the study between November 2012 and July 2013 by the Pediatric Departments of 'Sapienza' University of Rome. Each patient underwent a standardized general and neurological examination, an electroencephalogram, a questionnaire about neurological features and a validated questionnaire about SDB. We used OSA score = 1.42 D + 1.41 A + 0.71 S − 3.83, where D is difficulty breathing during sleep, A is apnea observed during sleep, and S is snoring. Values assigned to D and S were 0, never; 1, occasionally; 2, frequently; and 3, always. Values assigned to A were 0, no; and 1, yes. OSA scores < 0 predict normality; values > 0 predict OSA.[7]

Diagnosis of headache was made according to the International Classification of Headache Disorders.[8]

All of the patients received a GFD and after 6 months each one was revaluated with general and neurological examination and the above-mentioned questionnaires; thereafter, patients with abnormalities at the first awake-EEG exam underwent a new EEG investigation. Parents confirmed the complete adherence to the GFD.

Informed consent was obtained from parents.

3. Results

At CD diagnosis all children had normal weight and negative neurological examination; none of them had allergic rhinitis and/or nasal congestion, tonsillar hypertrophy was observed only in a child. General and neurological exams remained unchanged after treatment. As shown in Table 1, the EEG examinations revealed abnormal finding, such as focal or generalized sharps and/or spikes and spike-waves, in nine children (47.4%) without clear recognizable clinical manifestations. The questionnaire administered at CD diagnosis showed that seven patients (36.8%) complained headache that affected daily activities and 6 (31.6%) showed a positive OSA score.

The EEG abnormalities disappeared after 6 months of gluten exclusion in seven patients out of nine (77.7%); for example, see the patient number 10 before (A and B) and after (C) in Fig. 1.

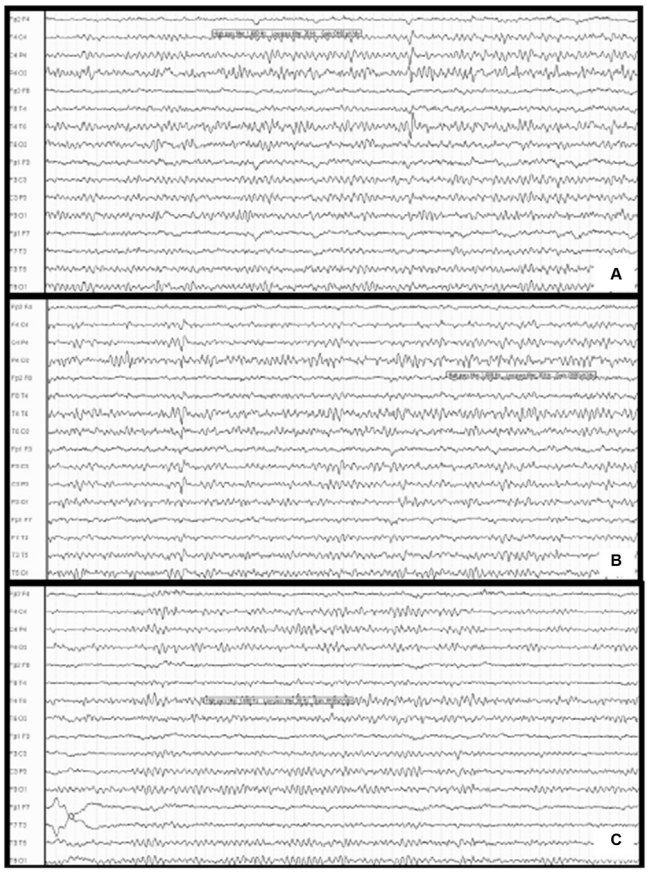

Fig. 1. EEG epochs of patient number 10 of Table 1 showing sharp and rare spikes in the right temporo-parietal region (A) with sporadic spreading (B) before the gluten-free diet and normal EEG recorded six months after the diet (C).

Parents of 1 child refused to perform the second EEG; in the last remaining child the EEG abnormalities did not change and they were related to the appearance of "Eyelid Myoclonia with Absences" (Jeavons Syndrome) which likely was not related to CD and not responsive to GFD.

After 6 months of GFD headache disappeared in five children out of seven (71.4%) and improved in the remaining two children. All children showed a negative OSA score after diet institution and without orthodontic, medical or surgical treatment.

Table 1
Patients with EEG abnormalities and/or headache and SDB at CD diagnosis and after 6 months of GFD. Patients without these features were not included.

Patient no.	Age at CD diagnosis, years	EEG abnormalities at CD diagnosis, yes (cerebral regions) or not	EEG abnormalities after GFD, yes (cerebral regions) or not	Headache at CD diagnosis, yes or not	Headache after GFD, yes or not	SDB at CD diagnosis, yes or not	SDB after GFD, yes or not
1	5.58	Yes (diffuse)	Not	Not	Not	Not	Not
2	7.91	Not	Not	Yes	Not	Yes	Not
3	9.75	Yes (occipital)	Not	Yes	Yes	Yes	Not
4	10.33	Yes (occipital)	Not	Not	Not	Not	Not
5	16.16	Yes (diffuse)	Not	Yes	Not	Not	Not
6	3.16	Yes (diffuse)	Not	Not	Not	Yes	Not
7	6.83	Yes (parietal)	Not	Yes	Yes	Not	Not
8	16.50	Not	Not	Yes	Not	Not	Not
9	7.42	Yes (frontal)	Yes	Not	Not	Yes	Not
10	14.16	Yes (diffuse)	Not	Not	Not	Not	Not
11	4.33	Not	Not	Yes	Not	Yes	Not
12	7.00	Not	Not	Yes	Not	Not	Not
13	8.67	Yes (diffuse)	*	Not	Not	Yes	Not

* Parents refused to perform the second EEG.

4. Discussion

This is the first prospective trial aimed to investigate the presence of EEG abnormalities, neurological disorders and SDB in children with a new CD diagnosis before the GFD, and their response to the diet.

To the best of our knowledge, no studies have assessed yet the prevalence of subclinical EEG abnormalities and SDB in children and adolescents with newly diagnosed CD.

In 47.4% of children we detected EEG abnormalities, particularly focal or generalized sharps and/or spikes and spike-waves, without any clinical manifestations before GFD institution; EEG abnormalities disappeared after 6 months of gluten exclusion except for one child in which a clinical manifestation appeared related to EEG abnormalities at the second recording (the child affected by absence eyelid myoclonia).

The lack of study which aims to identify the prevalence of EEG subclinical abnormalities in newly diagnosed CD does not allow us to compare our data with other cohort of children. However, it is important to note that our findings about the localization of EEG abnormalities (diffuse, occipital, parietal, and frontal regions) are in contrast with previous studies since they have demonstrated the major involvement of the occipital lobe in epilepsy related to CD.[9]

In the other hand a recent study showed that the prevalence of CD was higher than the normal population among children with occipital lobe epilepsy, therefore it is recommended to screen for CD in these patients.[10]

Data on the prevalence of headache in CD patients are controversial: Lahat et al.[11] did not find a significant association, while Lionetti et al.[12] showed a prevalence of 24.8% in a small series of CD children vs 8% in healthy children and the amelioration of headache in 76.4% of children on GFD.

Our results show that 36.8% of our CD patients complained headache. The symptom disappeared in 71.4% of them and ameliorated in the remaining children after GFD institution. It is interesting that not a single patient had clinical seizures and in regard to this we have previously hypothesized that the onset of clinical symptoms (such as convulsions and other neurological features) may be preceded by a period in which neuronal hyperexcitability is expressed exclusively by subclinical electroencephalic abnormalities.[13]

In this matter there is evidence suggesting that the efficacy of a GFD is inversely related to the duration of neurological disorders before the initiation of a GFD as well as to the age of the patient at the start of the GFD.[14]

However, the pathogenesis of neurological manifestations in CD has yet to be fully understood but immunological, nutritional and toxic mechanisms have been suggested.

At the same time we believe that a condition of chronic inflammation such as CD may be a predisposing factor for the development of SDB and our results (31.6% of children presented a positive OSA score at CD diagnosis, while in general population the prevalence of OSA is 1–5.7%) confirm this hypothesis. Surprisingly after the diet all patients had negative OSA score without any other treatment.

Our study presents several limitations: we enrolled a small sample size and we did not perform the magnetic resonance imaging; further studies on larger series of children are warranted to confirm our preliminary results.

It would also be interesting to compare the prevalence of subclinical EEG abnormalities in this group of children with the prevalence of the sporadic abnormalities found in a small portion of the healthy pediatric population[15] and to monitor any abnormalities over time.

According to our preliminary data, in the presence of unexplained EEG abnormalities and/or other neurological disorders/SDB an atypical or silent CD should also be taken into account.

Conflict of interest statement

None declared.

References

1. Bonamico M, Nenna R, Montuori M, Luparia RP, Turchetti A, Mennini M, et al. First salivary screening of celiac disease by detection of anti-transglutaminase autoantibody radioimmunoassay in 5000 Italian primary school children. *J Pediatr Gastroenterol Nutr* 2011;**52**:17–20.
2. Bushara KO. Neurologic presentation of celiac disease. *Gastroenterology* 2005;**128**:S92–7.
3. Diaconu G, Burlea M, Grigore I, Anton DT, Trandafir LM. Celiac disease with neurologic manifestations in children. *Rev Med Chir Soc Med Nat Iasi* 2013; **117**:88–94.
4. Hijaz NM, Bracken JM, Chandratre SR. Celiac crisis presenting with status epilepticus and encephalopathy. *Eur J Pediatr* 2013 [Epub ahead of print].
5. Lionetti E, Francavilla R, Pavone P, Pavone L, Francavilla T, Pulvirenti A, et al. The neurology of coeliac disease in childhood: what is the evidence? A systematic review and meta-analysis. *Dev Med Child Neurol* 2010;**52**:700–7.
6. Marcus CL, Brooks LJ, Draper KA, Gozal D, Halbower AC, Jones J, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* 2012;**130**:714–55.
7. Brouilette R, Hanson D, David R, Klemka L, Szatkowski A, Fernbach S, et al. A diagnostic approach to suspected obstructive sleep apnea in children. *J Pediatr* 1984;**105**:10–4.
8. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders: 2nd edition. *Cephalalgia* 2004;**24**(Suppl. 1):9–160.
9. Licchetta L, Bisulli F, Di Vito L, La Morgia C, Naldi I, Volta U, et al. Epilepsy in coeliac disease: not just a matter of calcifications. *Neurol Sci* 2011;**32**:1069–74.
10. Dai AI, Akcali A, Varan C, Demiryürek AT. Prevalence of resistant occipital lobe epilepsy associated with celiac disease in children. *Childs Nerv Syst* 2014;**30**: 1091–8.
11. Lahat E, Broide E, Leshem M, Evans S, Scapa E. Prevalence of celiac antibodies in children with neurologic disorders. *Pediatr Neurol* 2000;**22**:393–6.
12. Lionetti E, Francavilla R, Maiuri L, Ruggeri M, Spina M, Pavone P, et al. Headache in pediatric patients with celiac disease and its prevalence as a diagnostic clue. *J Pediatr Gastroenterol Nutr* 2009;**49**:202–7.
13. Ferretti A, Parisi P, Villa MP. The role of hyperhomocysteinemia in neurological features associated with coeliac disease. *Med Hypotheses* 2013;**81**:524–31.
14. Mavroudi A, Karatza E, Papastavrou T, Panteliadis C, Spiroglou K. Successful treatment of epilepsy and celiac disease with a gluten-free diet. *Pediatr Neurol* 2005;**33**:292–5.
15. Capdevila OS, Dayyat E, Kheirandish-Gozal L, Gozal D. Prevalence of epileptiform activity in healthy children during sleep. *Sleep Med* 2008;**9**:303–9.